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Reactions of some Quinazoline Compounds with Ethoxymethylenemalonic Acid Derivatives

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The reactions of ethyl (1,4-dihydro-4-oxoquinazolin-2-yl)acetate **4** and 2-aminoquinazolin-4(1*H*)-one **5** with diethyl ethoxymethylenemalonate (EMME), (ethoxymethylene)malononitrile (EMMN) and ethyl (ethoxymethylene)cyanoacetate (EMCA) are reported, and rather different results are obtained to those previously found with quinoline analogs. Reaction of **4** with EMME gives a pyrido[1,2-*a*]quinazoline, while with EMMN and EMCA ethyl 2-(pyridin-2-yl)aminobenzoates are formed, presumably by ring-opening of intermediate pyrido[2,1-*b*]quinazolines. Reaction of **5** with EMME likewise results in ultimate cyclization onto N-1 of the quinazoline, while the EMMN and EMCA reactions give isolable pyrimido[2,1-*b*]quinazolines. These are readily cleaved under mild conditions.

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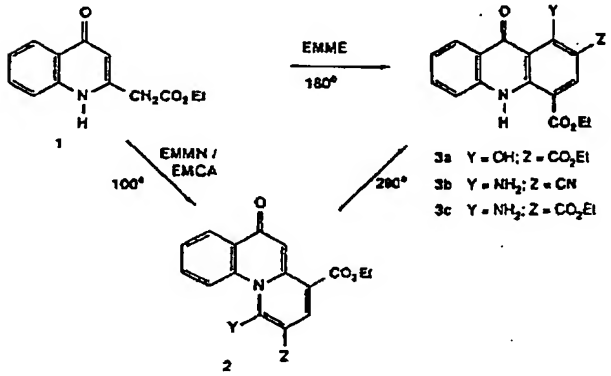
We recently showed that reactions of ethyl (1,4-dihydro-4-oxoquinolin-2-yl)acetate **1** with the malonic acid derivatives diethyl ethoxymethylenemalonate (EMME), (ethoxymethylene)malononitrile (EMMN) and ethyl (ethoxymethylene)cyanoacetate (EMCA) gave facile syntheses of benzo[*b*]quinolizines **2** or acridines **3**, depending on reagent and conditions [1].



The ease of ring closure onto C-3 of the quinoline ring was of particular interest and appeared to be a consequence of the presence of the 4-oxo group. It was therefore thought worthwhile to check on the effect of replacing the 3-CH group by N, compound **4**, which might provide simple entry into other tricyclic heterocycles of interest. Significantly different behaviour to that observed for **1** has been found.

As reactions of arylamines with EMME *etc.* are standard methods of heterocycle formation [2], compound **5**, which had not previously been investigated in such reactions, was included for comparison.

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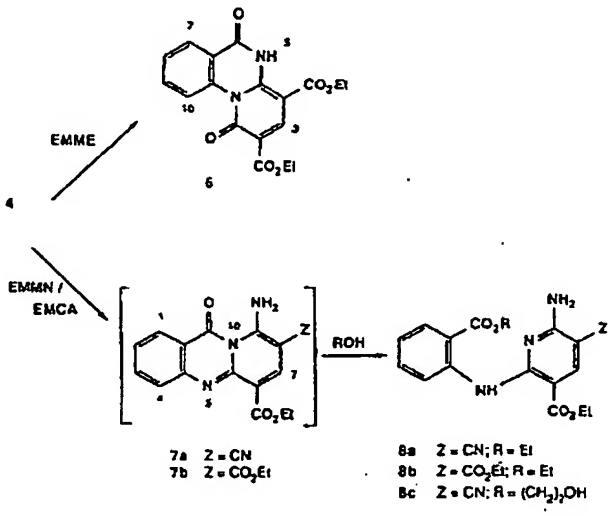
Quite different behaviour to that of **1** was observed. In this case, reaction with EMME (no solvent) at 180° gave a good yield of a single product **6**, where cyclization occurred onto position N-1 rather than N-3 of the quinazoline ring. This assignment is based on the low field ^{1}H nmr signal of H-10, due to the proximity of the carbonyl group. This was previously noted as characteristic of such angular ring systems and was absent in linear acridinones [1] [3]. This preparation provides a simple entry to the pyrido[1,2-*a*]quinazoline system, for which there are few reported syntheses [4].



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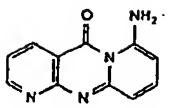

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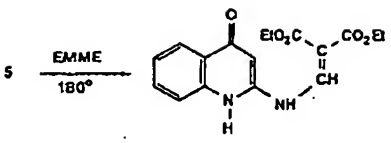

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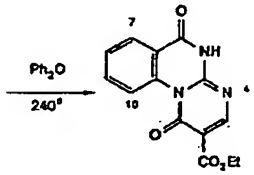

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Reaction with EMMN or EMCA also gave different behaviour to that observed with the quinoline compound. Reaction with EMMN as before [1] (no solvent, 100°) gave a mixture from which a small amount of compound was isolated, which had a ^1H nmr spectrum as expected of a cyclized compound but which contained an extra ethanol moiety. When the reaction was carried out in ethanol, this compound, identified as **8a** by X-ray crystallography, was formed in good yield. Reaction of **4** with EMCA gave the analogous **8b**, while **8c** was formed from EMMN in ethanediol solvent.

These compounds were thermally quite stable. Compound **8a** melted at 78-79° and then resolidified; the spectrum was unchanged and this appeared to just have been a change in crystalline form (the relevance of this observation will be seen regarding **5** below).

The formation of **8** are best explained by intermediate formation of the linear tricycle **7** which then readily breaks down in a reaction with the solvent. This seems more plausible than an angular intermediate analog of **2**. If so, cyclization in the quinazoline series follows the opposite path to that in the quinoline. Though various conditions were tried, we were not able to obtain any direct evidence for **7**.

Pyrido[2,1-*b*]quinazolin-11-ones are readily cleaved in the centre ring, as suggested here, by alkaline hydrolysis, while the ring reforms when the 2-(2-pyridinylamino)benzoic acid so formed is heated above its melting point [5]. A related compound, **9**, gave an analogous methyl ester on simply being stirred with methanol at room temperature [6]. The apparent instability of **7** in hot ethanol is therefore reasonable, though the refusal of **8** to recyclize at

Table 1

Crystal Data for 8a

Chemical formula	$C_{16}H_{12}N_4O_4$
Formula weight	354.4
Crystal system	triclinic
Space group	$P\bar{1}$
a (Å)	11.921(1)
b (Å)	12.076(1)
c (Å)	13.155(1)
α (deg)	81.49(1)
β (deg)	98.24(1)
γ (deg)	101.37(1)
V (Å^3)	1823.4(3)
Z	4
D_m (g cm^{-3})	1.30(1)
D_c (d cm^{-3})	1.291
F (000)	744
λ (Å)	1.5418
μ (CuKα) (cm^{-1})	6.89
Crystal size (mm)	0.26 x 0.63 x 0.26
T (K)	289(1)

elevated temperatures was a little surprising. It is suggested that the ready ring opening of **7** is due to steric interaction of the carbonyl group with the 9-amino substituent, buttressed as the latter is by the 8-substituent. The pyridine nitrogen in **8** would likewise be hindered to cyclization by attack on the ester carbonyl carbon.

The X-ray analysis of **8a** revealed two independent molecules in the crystal, both of which have similar conformations. In both the molecules, the C, N and O atoms lie close to two planes, each of which includes the bridging ni-

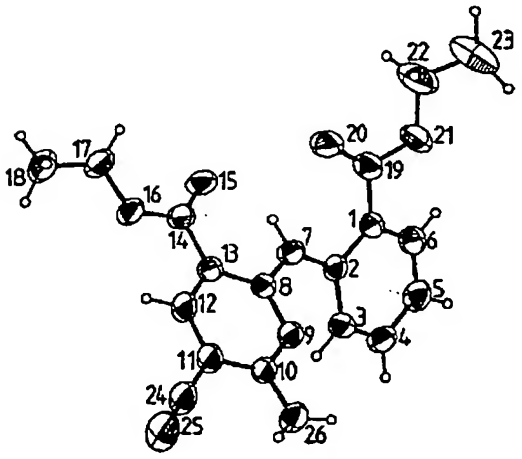

Figure 1. ORTEP drawing of **8a**. Thermal ellipsoids are scaled to the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary radii.

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Table 2

Final Atomic Coordinates for 8a and Isotropic Temperature Factors.
Atoms 1 to 26 (molecule 1) and Atoms 31 to 56 (molecule 2). E.s.d. Values are Given in Parentheses

Atom	10^4X/a	10^4Y/b	10^4Z/c	B_{eq}*	Atom	10^3X/a	10^3Y/b	10^3Z/c	B_{iso}
C(1)	3262(1)	1755(1)	6201(1)	3.26(3)	H(3)	367(2)	385(2)	431(1)	3.5(4)
C(2)	3277(1)	2292(1)	5175(1)	3.09(3)	H(4)	427(2)	485(2)	571(2)	5.1(5)
C(3)	3679(2)	3467(1)	5013(1)	3.48(3)	H(5)	420(2)	400(2)	748(2)	5.6(5)
C(4)	4018(2)	4082(2)	5836(1)	3.85(3)	H(6)	358(2)	207(2)	769(2)	5.4(5)
C(5)	3972(2)	3563(2)	6846(1)	4.13(3)	H(7)	220(2)	112(2)	443(2)	5.4(5)
C(6)	3615(2)	2410(2)	7016(1)	3.89(3)	H(12)	207(2)	139(2)	98(2)	4.4(4)
N(7)	2821(1)	1664(1)	4348(1)	3.57(2)	H(17a)	−90(2)	−3(2)	239(2)	5.3(5)
C(8)	3080(2)	1878(1)	3352(1)	3.17(3)	H(17b)	−37(2)	−116(2)	245(2)	5.5(5)
N(9)	4079(1)	2575(1)	3176(1)	3.36(2)	H(18a)	−113(2)	4(2)	55(2)	7.5(7)
C(10)	4352(1)	2838(1)	2208(1)	3.29(3)	H(18b)	−62(2)	−112(2)	64(2)	6.9(6)
C(11)	3613(2)	2418(2)	1356(1)	3.67(3)	H(18c)	−186(2)	−110(2)	108(2)	6.6(6)
C(12)	2610(2)	1674(2)	1556(1)	3.68(3)	H(22a)	334(3)	−153(3)	725(3)	9.6(10)
C(13)	2317(2)	1362(1)	2548(1)	3.28(3)	H(22b)	215(4)	−137(3)	759(3)	11.6(12)
C(14)	1230(2)	590(1)	2737(1)	3.50(3)	H(23a)	448(4)	−90(3)	878(3)	12.4(11)
O(15)	921(1)	272(1)	3593(1)	4.57(2)	H(23b)	336(3)	−83(3)	927(3)	9.7(9)
O(16)	603(1)	259(1)	1882(1)	3.92(2)	H(23c)	327(3)	−217(3)	908(2)	9.2(8)
C(17)	−518(2)	−452(2)	2027(2)	4.37(3)	H(26a)	585(2)	369(2)	268(2)	5.7(5)
C(18)	−1112(2)	−689(2)	980(2)	5.09(4)	H(26b)	557(2)	363(2)	147(2)	5.6(5)
C(19)	2876(2)	511(2)	6430(1)	3.99(3)	H(33)	1085(2)	705(2)	289(2)	4.7(5)
O(20)	2228(1)	−80(1)	5860(1)	5.58(3)	H(34)	1191(2)	795(2)	161(2)	5.2(5)
O(21)	3312(1)	108(1)	7366(1)	5.44(3)	H(35)	1128(2)	766(2)	−16(2)	4.9(5)
C(22)	2998(4)	−1118(2)	7686(2)	7.03(6)	H(36)	952(2)	640(2)	−51(2)	5.6(5)
C(23)	3490(4)	−1324(3)	8776(2)	8.28(8)	H(37)	840(2)	505(2)	265(2)	4.6(5)
C(24)	3917(2)	2751(2)	330(1)	4.77(4)	H(42)	848(2)	487(2)	616(1)	3.6(4)
N(25)	4176(2)	3043(2)	−482(1)	7.23(4)	H(47a)	716 (3)	184(3)	476(2)	8.2(8)
N(26)	5359(1)	3541(2)	2085(1)	4.33(3)	H(47b)	597(3)	237(3)	472(2)	9.1(8)
C(31)	9147(2)	6004(1)	976(1)	3.47(3)	H(48a)	728(3)	153(3)	660(2)	9.1(9)
C(32)	9535(2)	6193(1)	2010(1)	3.23(3)	H(48b)	619(3)	205(3)	661(3)	10.7(11)
C(33)	10586(2)	6925(2)	2207(1)	3.85(3)	H(48c)	608(2)	92(3)	607(2)	7.5(7)
C(34)	11212(2)	7475(2)	1414(2)	4.51(4)	H(52a)	613(2)	466(2)	−56(2)	6.0(6)
C(35)	10821(2)	7302(2)	404(1)	4.85(4)	H(52b)	693(2)	370(2)	−41(2)	5.1(5)
C(36)	9810(2)	6570(2)	190(1)	4.31(4)	H(53a)	693(3)	549(3)	−224(3)	10.5(9)
N(37)	8911(1)	5603(1)	2819(1)	3.28(3)	H(53b)	770(3)	446(2)	−203(2)	7.8(7)
C(38)	8978(1)	5877(1)	3799(1)	2.92(3)	H(53c)	643(3)	405(2)	−222(2)	7.5(7)
N(39)	9491(1)	6929(1)	3974(1)	3.31(3)	H(56a)	1036(2)	876(2)	450(2)	6.2(6)
C(40)	9656(2)	7219(1)	4930(1)	3.40(3)	H(56b)	1024(2)	854(2)	568(2)	5.0(5)
C(41)	9321(2)	6423(1)	5794(1)	3.26(3)					
C(42)	8731(1)	5367(1)	5597(1)	3.18(3)					
C(43)	8510(1)	5057(1)	4606(1)	2.93(3)					
C(44)	7812(1)	3959(1)	4401(1)	3.23(3)					
O(45)	7506(1)	3656(1)	3552(1)	4.34(2)					
O(46)	7491(1)	3303(1)	5267(1)	4.08(2)					
C(47)	6746(2)	2215(2)	5122(2)	4.99(5)					
C(48)	6524(3)	1617(3)	6161(2)	6.94(6)					
C(49)	8076(2)	5207(2)	675(1)	3.61(3)					
O(50)	7507(1)	4544(1)	1264(1)	4.89(3)					

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Table 2 (continued)

Atom	10^4X/a	10^4Y/b	10^4Z/c	B_{eq}*	Atom	10^3X/a	10^3Y/b	10^3Z/c	B_{iso}
O(51)	7818(1)	5288(1)	−344(1)	4.72(3)					
C(52)	6848(2)	4507(2)	−775(2)	4.97(4)					
C(53)	6936(3)	4627(3)	−1912(2)	5.79(5)					
C(54)	9609(2)	6755(2)	6810(1)	4.04(3)					
N(55)	9872(2)	7081(2)	7599(1)	6.08(4)					
N(56)	10145(2)	8291(1)	5047(1)	4.99(4)					

*$B_{eq} = 8/3\ \pi^2 \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$

Table 3

Bond Lengths (Å) and Angles (°) for 8a. E.s.d. Values are Given in Parentheses

Atoms	Molecule 1	Molecule 2	Atoms	Molecule 1	Molecule 2
C(1) - C(2)	1.409(2)	1.409(2)	C(11) - C(12)	1.379(3)	1.371(2)
C(1) - C(6)	1.394(2)	1.405(2)	C(11) - C(24)	1.427(2)	1.428(2)
C(1) - C(19)	1.481(3)	1.482(3)	C(12) - C(13)	1.378(2)	1.384(2)
C(2) - C(3)	1.400(2)	1.399(3)	C(13) - C(14)	1.469(3)	1.459(2)
C(2) - N(7)	1.402(2)	1.410(2)	C(14) - O(15)	1.219(2)	1.211(2)
C(3) - C(4)	1.372(2)	1.382(3)	C(14) - O(16)	1.326(2)	1.345(2)
C(4) - C(5)	1.386(2)	1.376(3)	O(16) - C(17)	1.460(2)	1.455(2)
C(5) - C(6)	1.368(3)	1.367(3)	C(17) - C(18)	1.496(4)	1.482(4)
N(7) - C(8)	1.365(2)	1.365(2)	C(19) - O(20)	1.201(2)	1.206(2)
C(8) - N(9)	1.344(2)	1.334(2)	C(19) - O(21)	1.327(2)	1.325(2)
C(8) - C(13)	1.425(2)	1.435(2)	O(21) - C(22)	1.467(3)	1.445(2)
N(9) - C(10)	1.337(2)	1.332(2)	C(22) - C(23)	1.474(4)	1.498(4)
C(10) - C(11)	1.414(2)	1.425(2)	C(24) - N(25)	1.141(2)	1.144(2)
C(10) - C(26)	1.342(2)	1.332(2)			
C(2)-C(1)-C(6)	119.2(1)	119.2(1)	C(10)-C(11)-C(12)	117.8(1)	117.4(1)
C(2)-C(1)-C(19)	121.4(1)	122.9(1)	C(10)-C(11)-C(24)	120.3(3)	119.2(1)
C(6)-C(1)-C(19)	119.4(1)	117.9(1)	C(12)-C(11)-C(24)	121.9(2)	123.4(1)
C(1)-C(2)-C(3)	118.4(1)	117.9(1)	C(11)-C(12)-C(13)	121.6(2)	121.9(1)
C(1)-C(2)-N(7)	119.9(1)	120.4(1)	C(8)-C(13)-C(12)	116.7(1)	116.6(1)
C(3)-C(2)-N(7)	121.6(1)	121.6(1)	C(8)-C(13)-C(14)	122.7(1)	122.3(1)
C(2)-C(3)-C(4)	120.5(1)	121.4(2)	C(12)-C(13)-C(14)	120.5(1)	121.1(1)
C(3)-C(4)-C(5)	121.2(2)	120.5(2)	C(13)-C(14)-O(15)	124.0(1)	125.3(1)
C(4)-C(5)-C(6)	118.8(2)	119.4(2)	C(13)-C(14)-O(16)	113.6(1)	112.8(1)
C(1)-C(6)-C(5)	121.7(2)	121.6(2)	O(15)-C(14)-O(16)	122.3(1)	121.9(1)
C(2)-N(7)-C(8)	128.3(1)	127.7(1)	C(14)-O(16)-C(17)	115.5(1)	116.1(1)
N(7)-C(8)-N(9)	117.2(1)	117.6(1)	O(16)-C(17)-C(18)	107.5(2)	107.5(2)
N(7)-C(8)-C(13)	120.4(1)	120.8(1)	C(1)-C(19)-O(20)	125.3(1)	125.6(1)
N(9)-C(8)-C(13)	122.4(1)	121.6(1)	C(1)-C(19)-O(21)	112.0(1)	111.4(1)
C(8)-N(9)-C(10)	119.3(1)	120.2(1)	O(20)-C(19)-O(21)	122.7(1)	123.0(1)
N(9)-C(10)-C(11)	122.0(1)	121.7(1)	C(19)-O(21)-C(22)	117.4(2)	118.7(1)
N(9)-C(10)-N(26)	116.3(1)	117.2(1)	O(21)-C(22)-C(23)	106.6(2)	106.1(2)
C(11)-C(10)-N(26)	121.6(1)	121.1(1)	C(11)-C(24)-N(25)	178.2(2)	176.0(2)

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trogen, N(7), and one aromatic ring plus its substituents (Figure 1). The dihedral angles between the ring planes are 138 and 149° in molecules **1** and **2** respectively. The torsion angles C(2)-N(7)-C(8)-C(9) and C(3)-C(2)-N(7)-C(8) with the respective values of +19 [7] and +29° (molecule 1), and +16 and +22° (molecule 2) define a twist conformation for the bridged aromatic rings with the bulky ester functions *ortho* to N(7) in the *distal* positions. The comparable bond lengths and angles in the two independent molecules are in good agreement (Table 3). Note that this structure has the pyridine nitrogen distant from the ester carbonyl group which would be involved in a cyclization reaction.

In the crystal, the molecules are linked into chains along the [110] direction by four unique intermolecular hydrogen bonds (Figure 2). For these interactions, the exocyclic amino groups are hydrogen bonded to the two carbonyl oxygens of the ester groups of an adjacent molecule. The H-bonding dimensions are given in Table 4. Each molecular chain is composed of one mirror image conformer only.

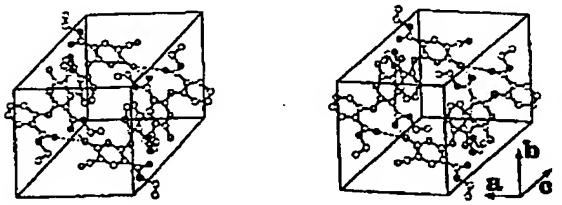

Figure 2. Stereoview of the crystal packing of **8a**.

Reaction of Aminoquinazolinone **5** with EMME.

The initial reaction with EMME at 180° was quite facile, but only proceeded to the intermediate, **10**, in contrast to reactions of the acetate esters **1** and **4**. Thermal cyclization to **11** was readily achieved in diphenyl ether at 240° (better than paraffin which gave a lower yield and the product was impure). A single mode of cyclization was followed, onto N-1 of the quinazoline, as indicated by the low field shift of the H-10 signal in the ^{1}H nmr spectrum of the product. This behaviour accords with that of the acetate ester **4** above in its reaction with EMME.

Reaction of Aminoquinazoline **5** with EMMN/EMCA.

Reactions with these two reagents were similar, but with surprising internal differences, with the overall pattern resembling that for the acetate esters. The high melting point and low solubility of **5** did not allow reactions with neat EMMN or EMCA, as previously, or in common solvents. Ethanediol was successfully used and, at 100°, solid separated from each reaction mixture within 1 hour.

This initial product from the EMCA reaction was obtained as an isomeric mixture (1.5:1), which still contained ethyl and cyano functions, and was assigned structure **12a**. No further reaction occurred under these conditions. The analogous intermediate presumably forms in the EMMN reaction but is evidently more reactive as the initial ethanediol insoluble product incorporated a molecule of ethanediol and was assigned structure **14** by analogy with the formation of **8** from the acetate ester. Compound **13** is therefore proposed as the undetected precursor of **14**.

These intermediates underwent rapid cyclization at 240-270° (see Experimental for conditions) with the formation of high-melting, yellow products, assigned structures **15**. The ^{1}H nmr pattern for the aromatic protons of the two compounds were identical and different from either **12** or **14**. The cyclization of **14** is significant (note the difference to the stability of **8**) as the product can only be a linear tricycle.

Table 4

Hydrogen Bonding Dimensions for **8a**. Distances (Å) and Angles (°).

Atoms	N.....O	N-H	H...O	<N-H...O	Symmetry Operation
N(26).....O(45)	2.969(2)	0.93(2)	2.14(2)	149(2)	None
N(26).....O(50)	2.894(2)	0.87(3)	2.39(2)	117(2)	None
N(56).....O(15)	2.918(2)	0.89(2)	2.08(2)	159(2)	1 + *x*, 1 + *y*, *z*
N(56).....O(20)	3.019(2)	0.91(2)	2.62(2)	108(1)	1 + *x*, 1 + *y*, *z*

Two structures, **13** or **15**, are possible, however, depending on which pyrimidine N is involved. We prefer **15** for the following reasons:

(i) The ^{1}H nmr signal for H-4 is at a significantly lower field than for any other like proton in the series we have investigated (such as **12** and **14**), attributable to the adjacent carbonyl function.

(ii) Of the two pyrimidine nitrogens in **14**, that *para* to the amino group would be more nucleophilic and less hindered.

(iii) The cyclization of **14** but not of **8** (where such a ring nitrogen is absent) also suggests that this nitrogen is involved. If this assignment is correct, **12a** cannot lead directly to **15a** and it is necessary to postulate a rearrangement occurring along this route.

The exact form of compounds **15** in dimethyl sulfoxide is not known; the ^{1}H nmr spectrum showed two slightly broadened single peaks in the aromatic region, in addition to those for the ring protons. These peaks were maintained, though shifted downfield by 1.5 ppm, on the addition of a few drops of trifluoracetic acid. Structures **15** would not be expected to show two distinct NH signals.

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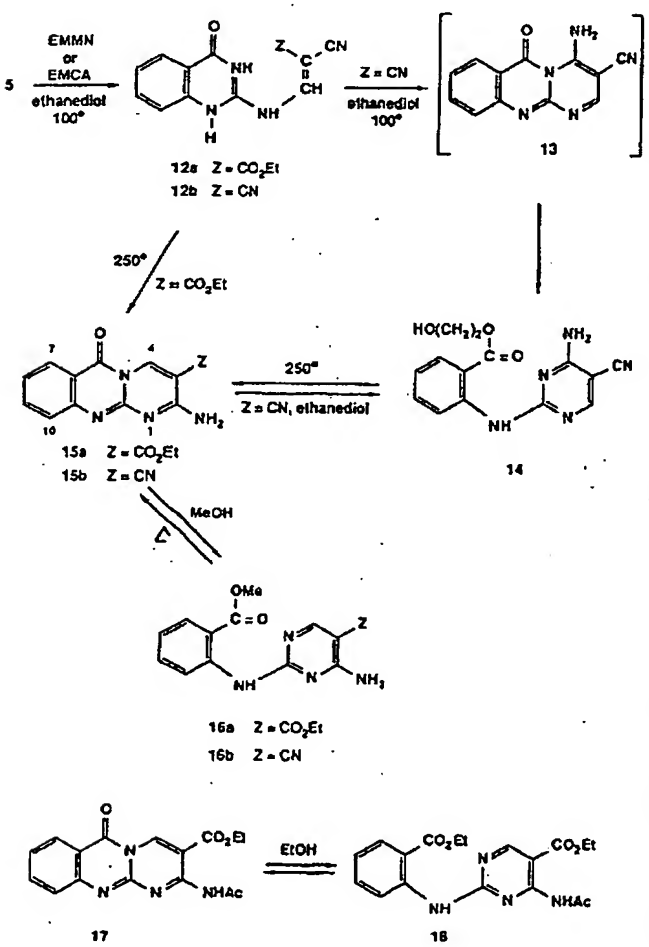
The pyrimido[2,1-*b*]quinazolin-6-one system, **15**, is known and is readily formed from *N*-pyrimidinylanthranilic acids (as would be derived from **14**), especially if a position next to N is unsubstituted, and the ring opens again under hydrolytic conditions [8]. Compounds **15** underwent solvolytic ring opening quite readily. Thus, boiling methanol converted **15a** to the methyl ester **16a**, in a few minutes, while the much less soluble **15b** required a longer reaction time. In ethanediol at 100°, **15b** did dissolve and revert to **14** which precipitated from the solution as it formed.

The ease of the ring opening-ring closing process was more conveniently demonstrated for the more soluble acetyl derivative **17**. Dissolution of **17** in hot ethanol caused rapid ring opening to **18**. However, recyclization occurred while the ^{1}H nmr spectrum was being recorded in chloroform, and a c 1:1 equilibrium mixture was established within 30 minutes.

This work has revealed some interesting differences between quinoline and quinazoline compounds in reactions with EMME and related compounds and, in the preparation of **6** and **15**, has allowed an alternative route to some highly substituted derivatives of interesting tricyclic systems. The substituted hetaryl derivatives of the anthranilic acids so readily produced in the ring opening reactions are also of interest since related compounds have previously been found to be pharmacologically active [8].



EXPERIMENTAL

Reaction of 4 with EMME.

A mixture of **4** [9] (0.5 g) and EMME (0.42 g) was heated at 180° for 1 hour. This solidified on cooling and was filtered with the aid of some cold acetone to give **6** (0.6 g, 80%), mp 208-209° (from toluene); ^{1}H nmr (deuteriochloroform): 200 MHz, δ 1.39, 1.42 (t + t, 6H, CH_3CH_2, J = 7 Hz), 4.36, 4.40 (q + q, 4H, CH_2CH_3, J = 7 Hz), 7.33-7.84 (m, 2H, H-8,9), 8.22 (d, 1H, H-7, J = 8 Hz), 8.71 (s, 1H, H-3), 9.06 (d, 1H, H-10, J = 8 Hz), 12.9 (br s, 1H, NH). An analytical sample was further purified by passing through a short alumina column, using chloroform as the eluent.

Anal. Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.7; H, 4.53; N, 7.9. Found: C, 60.7; H, 4.2; N, 7.8.

Reaction of 4 with EMMN.

(a) In Ethanol.

Compound **4** (1.0 g) and EMMN (0.53 g) in ethanol (20 ml) was heated under reflux for 3 hours and the ethanol was then distilled off. The residue was extracted with hot toluene, filtered while hot, and the filtrate concentrated and cooled to give **8a** (1.4 g, 91%) as white crystals, mp 70-75° (then resolidified and melted again at 151-152°); ^{1}H nmr (deuteriochloroform): 400 MHz, δ 1.37, 1.39 (t + t, 6H, CH_3CH_2, J = 7 Hz), 4.39 (q + q, 4H, CH_2CH_3, J = 7 Hz), 5.36 (br s, 2H, NH_2), 7.12 (t, 1H, H-5, J = 8 Hz), 7.47 (t, 1H, H-4, J = 8 Hz), 8.0 (d, 1H, H-3, J = 8 Hz), 8.2 (d, 1H, H-6, J = 8 Hz), 8.33 (s, 1H, HetH), 11.9 (s, 1H, NH). A sample for analysis was further recrystallized from methanol.

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: C, 61.0; H, 5.1; N, 15.8. Found: C, 61.2; H, 5.0; N, 15.6.

(b) In Ethanediol.

The mixture was heated at 100° for 1.5 hours, cooled, and water was added to give the pale yellow **8c**, mp 151-152° (from toluene) in 60% yield. ^{1}H nmr (deuteriochloroform) 400 MHz, δ 1.39 (t, 3H, CH_3CH_2, J = 7 Hz), 3.82-3.95 (t, 2H, CH_2OH, J = 7 Hz) 4.35-4.5 (m, 4H, CH_2CH_3 + OCH_2), 6.36 (br s, 2H, NH_2), 7.17 (t, 1H, H-5, J = 8 Hz), 7.57 (t, 1H, H-4, J = 8 Hz), 8.14 (d, 1H, H-3, J = 8 Hz), 8.3 (d, 1H, H-6, J = 8 Hz), 8.37 (s, 1H, HetH), 11.8 (s, 1H, NH).

Reaction of 4 with EMCA.

This was carried out in ethanol as for the EMMN reaction and gave **8b** as white crystals, mp 170-171° (from ethanol); ^{1}H nmr (deuteriochloroform): 400 MHz, δ 1.3-1.4 (t + t + t, 9H, CH_3CH_2, J = 7 Hz), 4.3 (q, 2H, CH_2CH_3, J = 7 Hz), 4.4 (q + q, 4H, CH_2CH_3), 5.6 (br s, 1H, NH), 7.1 (t, 1H, H-5, J = 8 Hz), 7.45 (t, 1H, H-4, J = 8 Hz), 8.0 (d + br s, 2H, H-3 + NH), 8.4 (d, 1H, H-6, J = 8 Hz), 8.75 (s, 1H, HetH), 11.9 (s, 1H, NH).

Anal. Calcd. for $C_{20}H_{22}N_4O_4$: C, 59.85; H, 5.7; N, 10.5. Found: C, 59.9; H, 5.8; N, 10.3.

Reaction of 5 with EMME.

An equimolar mixture of **5** (prepared from guanidine carbonate and isatoic anhydride, as for the 6-nitro analog [10]) (1.0 g) and EMME (1.34 g) was heated at 180° for 1 hour during which time it gradually solidified. The solid was boiled with light petroleum, cooled and filtered to give **10** as a fawn solid (1.85 g, 90%), mp 213-215° (resolidifies) (from ethanol). ^{1}H nmr (deuteriochloroform): 90 MHz, δ 1.3 (t, 6H, CH_3CH_2, J = 7 Hz), 4.2 (q + q, 4H, CH_2CH_3, J = 7 Hz), 7.2-7.9 (m, 3H, H-6,7,8), 8.0 (d, 1H, H-5, J = 8 Hz), 8.9 (d, 1H, NHCH=, J = 12 Hz), 10.45 (d, 1H, NH, J = 12 Hz).

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Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 58.0; H, 5.1; N, 12.7. Found: C, 58.1; H, 5.4; N, 12.9.

Cyclization of **10**.

Compound **10** (0.3g) was added to stirring diphenyl ether at 240°. After 1.5 minutes, the solution was cooled, a little light petroleum (bp 60-90°) was added and the solid filtered to give **11** (0.21 g, 81%), mp 242-244° (from toluene); ^{1}H nmr (DMSO-d_6): 200 MHz, δ 1.3 (t, 3H, CH_2CH_3, J = 7 Hz), 4.25 (q, 2H, CH_2CH_3, J = 7 Hz), 7.67 (t, 1H, H-8, J = 8 Hz), 7.89 (t, 1H, H-9, J = 8 Hz), 8.21 (d, 1H, H-7, J = 8 Hz), 8.48 (s, 1H, H-3), 9.13 (d, 1H, H-10, J = 8 Hz).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.9; H, 3.9; N, 14.7. Found: C, 59.0; H, 3.9; N, 15.0.

Reaction of **5** with EMMN.

Compound **5** (0.30 g) was dissolved in hot ethanediol (4 ml) and to this solution at 100° was added EMMN (0.23 g). The mixture was maintained at 100° for 1 hour during which time a pale yellow solid separated. This was filtered, washed with methanol, and recrystallized from toluene to give **14** (0.47 g, 84%), mp 248-250° (turned dark yellow, resolidified and had mp >330°); ^{1}H nmr (DMSO-d_6): 200 MHz, δ 3.7 (m, 2H, CH_2CH_2OH), 4.3 (t, 2H, CH_2CH_2OH, J = 7 Hz), 5.0 (t, 1H, OH, J = 7 Hz), 7.1 (t, 1H, H-5, J = 8 Hz), 7.6 (t, 1H, H-4, J = 8 Hz), 7.7 (br s, 2H, NH_2), 8.0 (d, 1H, H-3, J = 8 Hz), 8.4 (s, 1H, HetH), 8.75 (d, 1H, H-6, J = 8 Hz), 10.7 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.2; H, 4.3; N, 23.4. Found: C, 56.3; H, 4.1; N, 23.5.

Cyclization of **14**.

Compound **14** (0.5 g) was added in portions, with stirring, to paraffin (10 ml) at 270-280°. After 5 minutes at this temperature, the mixture was cooled, light petroleum (bp 60-90°) was added and the orange solid, **15b**, (0.3 g, 76%) was filtered, and had mp >330° (from dimethyl sulfoxide); ^{1}H nmr (DMSO-d_6): 400 MHz, δ 7.34 (t, 1H, H-8, J = 8 Hz), 7.5 (d, 1H, H-10, J = 8 Hz), 7.8 (t, 1H, H-9, J = 8 Hz), 8.0 (br s, 1H, NH), 8.13 (d, 1H, H-7, J = 8 Hz), 8.5 (br s, 1H, NH), 9.4 (s, 1H, H-4); ir (potassium bromide): ν 3380, 3100 (br), 2240, 1725, 1665 cm^{-1}. The cyclization was also achieved by heating the solid **14** at 270° in an open beaker.

Anal. Calcd. for $C_{12}H_7N_3O$: C, 60.7; H, 3.0; N, 29.5. Found: C, 60.4; H, 3.0; N, 29.7.

Reaction of **15b** with Methanol.

A slurry of **15b** (0.15 g) in methanol (20 ml) was heated under reflux for 1 hour and filtered while hot. This process was repeated three times on the unreacted **15b**. The combined methanol extracts were evaporated and the residue recrystallized from methanol to give the cream **16b** (0.08 g), which darkened and changed form over the range 255-265°; ^{1}H nmr (DMSO-d_6): 200 MHz, δ 3.9 (s, 3H, OCH_3), 7.1 (t, 1H, H-5, J = 8 Hz), 7.6 (t, 1H, H-4, J = 8 Hz), 7.7 (br s, 2H, NH_2), 8.0 (d, 1H, H-3, J = 8 Hz), 8.45 (s, 1H, HetH), 8.75 (d, 1H, H-6, J = 8 Hz), 10.7 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 58.0; H, 4.1; N, 26.0. Found: C, 57.6; H, 4.0; N, 26.0.

Reaction of **15b** with Ethanediol.

A solution of **15b** (0.2 g) in ethanediol (2 ml) was heated at 100° for 1.5 hours during which time a solid separated. The cooled solution was diluted with methanol and filtered to give a quantitative yield of **14**.

Reaction of **5** with EMCA.

This was carried out as for the reaction with EMMN to produce, after recrystallization from a large volume of ethanol, an 85% yield of **12a**, as a mixture of isomers (A, B) (1.5:1), mp 198-199° (resolidified and melted again at 250°); ^{1}H nmr (DMSO-d_6): 400 MHz, δ 1.25 (t, 3H, CH_2CH_3 A, J = 7 Hz), 1.28 (t, 3H, CH_2CH_3 B, J = 7 Hz), 4.24 (q, 2H, CH_2CH_3 A, J = 7 Hz), 4.3 (q, 2H, CH_2CH_3 B, J = 7 Hz), 4.45 (br s, 4H, NH_2 A + B) 7.37 (t, 1H, H-7 A, J = 8 Hz), 7.39 (t, 1H, H-7 B, J = 8 Hz), 7.51 (d, 1H, H-8 A, J = 8 Hz), 7.54 (d, 1H, H-8 B, J = 8 Hz), 7.75 (t, 2H, H-6 A + B, J = 8 Hz), 8.0 (d, 1H, H-5 A, J = 8 Hz), 8.03 (d, 1H, H-5 B, J = 8 Hz), 8.6 (br s, 1H, -CH= A), 8.8 (s, 1H, -CH= B); ir (potassium bromide): 3210, 2220, 1690, 1650, 1620 cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.2; H, 4.2; N, 19.7. Found: C, 59.2; H, 4.6; N, 19.6.

Cyclization of **12a**.

When this isomeric mixture was heated in diphenyl ether, at 250°, for 5 minutes, the yellow **15a**, mp 250-251° (from dimethyl sulfoxide), was obtained in 93% yield; ^{1}H nmr (DMSO-d_6): 200 MHz, δ 1.38 (t, 3H, CH_2CH_3, J = 7 Hz), 4.4 (q, 2H, CH_2CH_3, J = 7 Hz), 7.32 (t, 1H, H-8, J = 8 Hz), 7.5 (d, 1H, H-10, J = 8 Hz), 7.8 (t, 1H, H-9, J = 8 Hz), 8.0 (br s, 1H, NH), 8.11 (d, 1H, H-7, J = 8 Hz), 8.6 (br s, 1H, NH), 9.3 (s, 1H, H-4); ir (potassium bromide): 3430, 3300-2900, 1710, 1650, 1605 cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.2; H, 4.2; N, 19.7. Found: C, 58.8; H, 4.3; N, 19.4.

Reaction of **15a** with Methanol.

Compound **15a** (0.4 g) dissolved in boiling methanol. After 15 minutes, the solution was cooled and **16a** (0.28 g, 64%), mp 170-172° (resolidified and melted again at 250-252°), separated and was collected; ^{1}H nmr (DMSO-d_6): 200 MHz, δ 1.36 (t, 3H, CH_2CH_3, J = 7 Hz), 3.93 (s, 3H, CH_3O), 4.32 (q, 2H, CH_2CH_3, J = 7 Hz), 7.0 (t, 1H, H-5, J = 8 Hz), 7.5 (t, 1H, H-4, J = 8 Hz), 8.0 (d, 1H, H-3, J = 8 Hz), 8.75 (s, 1H, HetH), 8.82 (d, 1H, H-6, J = 8 Hz), 10.9 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.0; H, 5.1; N, 17.7. Found: C, 57.0; H, 5.1; N, 17.9.

Acetylation of **15a**.

A mixture of **15a** (2.0 g) and acetic anhydride (5 ml) was heated under reflux for 15 minutes. Solid separated from the cooled solution. This was filtered, washed with light petroleum (bp 40-70°), and recrystallized from dioxan to give the lemon yellow **17** (1.6 g, 70%), mp 216-217°, which retained ½ molecule of dioxan even after vacuum drying; ^{1}H nmr (deuteriochloroform): 200 MHz, δ 1.45 (t, 3H, CH_2CH_3, J = 7 Hz), 2.72 (s, 3H, $COCH_3$), 3.7 (s, 4H, dioxan), 4.46 (q, 2H, CH_2CH_3, J = 7 Hz), 7.44 (t, 1H, H-8, J = 8 Hz), 7.7-7.9 (m, 2H, H-9,10), 8.3 (d, 1H, H-7, J = 8 Hz), 9.7 (s, 1H, H-4), 10.9 (br s, 1H, NH).

Anal. Calcd. for $C_{16}H_{14}N_4O_4 \cdot ½\ C_4H_8O_2$: C, 58.4; H, 4.9; N, 15.1. Found: C, 58.7; H, 5.0; N, 15.3.

Reaction of **17** with Ethanol.

When **17** was heated with ethanol for a few minutes and the solution concentrated, a solid, mp 189-190° (resolidified) was obtained. The ^{1}H nmr spectrum (deuteriochloroform): 200 MHz, changed quite rapidly with time, consistent with a change from **18** [δ 1.15 (t, 3H, CH_2CH_3, J = 7 Hz), 1.38 (t, 3H, CH_2CH_3, J = 7 Hz), 2.25 (s, 3H, $COCH_3$), 3.75 (q, 2H, CH_2CH_3, J = 7 Hz), 4.3 (q, 2H, CH_2CH_3, J = 7 Hz), 7.1 (s, 1H, HetH), 7.32 (t, 1H, H-5, J = 8 Hz), 7.5 (d, 1H, H-3, J = 8 Hz), 7.7 (t, 1H, H-4, J = 8 Hz), 8.2 (d, 1H, H-6, J = 8 Hz), 11.7 (br s, 1H, NH)] to **17** (peaks as above) and reached a 1:1 ratio within 30 minutes. Addition of drops of ethanol altered this ratio in favor of **18**.

X-Ray Analysis.

Compound **8a** formed prismatic crystals (elongated along the [010] direction) from acetone on evaporation. The crystal data are given in Table 1. The setting angles for 25 reflections, 41° < 2θ (CuKα) < 59°, were used to determine the cell parameters. Intensities were measured at 289(1) K on a Rigaku-AFC diffractometer with CuKα radiation (graphite-crystal monochromator, λ = 1.5418 Å). The data were recorded by an ω - 2θ scan with a range (Δω) of 1.2° + 0.5° tan θ and scan rate 2° min^{-1}. Three standard reflections monitored every 50 reflections showed no significant variation in intensity during the data collection. Data to a 2θ (max) of 130° yielded 5903 unique terms. The integrated intensities were corrected for Lorentz and polarization effects and for absorption (transmission factors ranged between 0.747 and 0.856).

The structure was solved by direct methods with SHELX76 [11], and

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all H atom sites were located on difference maps. Refinement with anisotropic temperature factors given to the C, N and O atoms and isotropic given to the H atoms, was carried out in two blocks, each block containing parameters for one molecule of the asymmetric unit. At convergence R = 0.048, R_w = 0.055 and S = 2.07 (defined as $[\Sigma w(\Delta F)^2/(N_o - N_p)]^{1/2}$ for 614 variables (N_p) and 5127 data (N_o) for which $I \geq \sigma I$. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ with $w = (\sigma^2|F_o| + 0.00035|F_o|^2)^{-1}$. An isotropic extinction correction of the form $F = F[1 - (1.025 \times 10^{-5}|F|^2/\sin\theta)]$ was applied to the calculated structure amplitudes. The largest peaks on the final difference map were of heights +0.24 and −0.25 e Å^{-3}, and the maximum shift-to-error ratio at convergence was 0.03:1. The atomic scattering factors used were those stored in SHELX76.

The final atomic coordinates are given in Table 2 and bond lengths and angles involving the non-hydrogen atoms are listed in Table 3. Figures 1 and 2 have been prepared from the output of ORTEP-II [12]. Anisotropic thermal parameters, short intermolecular contacts and listings of observed and calculated structure amplitudes are available as supplementary material.

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